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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
FALK, ANNE MARIE

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 12/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

SM.

Office Action Summary	Application No.	Applicant(s)	
	09/849,243	KIRSCHBAUM ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) *36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-35 and 37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5/01 and* 3/02.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The amendment filed August 7, 2001 has been entered. Claim 7 has been amended.

The preliminary remarks and Declaration under 37 CFR 1.132 filed March 15, 2002 have been entered.

The response to restriction requirement filed October 15, 2003 has been entered.

Applicants' election of Group I, Claims 1-35 and 37 in the response filed October 15, 2003 is acknowledged. Applicants state that the election is made with traverse. However, because Applicants did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). The elected invention is drawn to an epitope-tagged TBP transgenic animal, a method of making the transgenic animal, a method for isolating a higher order transcription complex, and a method for isolating a TAF or a TAF-interacting factor.

Claims 1-37 are pending in the instant application.

Claim 36 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention. Election was made **without** traverse in the response filed October 15, 2003.

Accordingly, Claims 1-35 and 37 are examined herein.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). The specific reference to any prior nonprovisional application must

include the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications except when the reference is to a prior application of a CPA assigned the same application number.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 1-35 and 37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to an epitope-tagged TBP transgenic animal, a method of making an epitope-tagged TBP transgenic animal, a method of expressing an epitope-tagged TBP in a transgenic animal, and a method for isolating a higher order transcription complex.

The specification fails to provide an enabling disclosure for the claimed transgenic animals, including the MT-hTBP and EF-hTBP transgenic mice disclosed in the working examples (pp. 29-41), because the only use contemplated for the epitope-tagged TBP transgenic animal is for the isolation of TBP-containing transcription complexes and the specification does not offer any guidance for preparing a transgenic animal that expresses the epitope-tagged TBP at a level sufficient to allow for the isolation of TBP-containing complexes. The specification reveals that, for the MT-hTBP transgenic mice, 35 transgene-positive founders were identified from 170 pups (p. 34, lines 26-27). For the EF-hTBP transgenic mice, 9 transgene-positive founders were identified from 76 pups (p. 34, lines 27-29). S1 nuclease protection assays revealed that, from 35 MT-hTBP founders, 7 showed detectable mRNA levels

(p. 37, lines 10-11) and, from 9 EF-hTBP founders, 3 showed detectable levels of mRNA (p. 37, lines 11-12). Thus, only a fraction of the transgene-positive mice expressed the transgene at the mRNA level. Example 8 provides a protocol for Western blot detection of transgenic protein (pp. 40-41). However, no results are provided. Thus it remains unclear as to whether any of the transgenic mice made actually expressed the epitope-tagged TBP. In the absence of expression of the epitope-tagged TBP, one would not be able to isolate higher order transcription complexes from the transgenic animals according to the claimed methods. Furthermore, the specification does not offer any guidance as to the level of expression of epitope-tagged TBP that would be required to permit isolation of TBP-containing complexes. One skilled in the art would expect that the endogenous murine TBP would compete with the heterologous epitope-tagged TBP expressed from the transgene (e.g., the human TBP) in forming the pre-initiation complex. In the absence of appropriate guidance, one skilled in the art would have been required to engage in undue experimentation to prepare transgenic animals from which higher order transcription complexes containing the epitope-tagged TBP could have been isolated.

The specification fails to provide an enabling disclosure for the preparation of any transgenic animal, including a transgenic mouse, of the type claimed because the phenotype of a transgenic animal cannot be predicted. Furthermore, the phenotype of a transgenic animal cannot be predicted based on the phenotype of another similarly constructed transgenic animal. While the specification discloses MT-hTBP and EF-hTBP transgenic mice that express the transgenic mRNA in an unspecified tissue of the mouse, the phenotype of any other species of animal harboring a similar transgene construct or other types of transgene constructs as recited in the claims, cannot be predicted. Furthermore, as discussed above, the specification does not teach how to obtain expression of an epitope-tagged TBP at a level sufficient to allow for the isolation of TBP-containing complexes in any animal. The specification does not teach what phenotype would be expected in any species of transgenic animal. No guidance is provided with regard to how one would have prepared any transgenic animals, other than mice. The mere

capability to perform gene transfer in any given species is not enabling for the claimed transgenic animals because the desired phenotype cannot be predictably achieved by simply introducing transgene constructs of the types recited in the claims. While gene transfer techniques are well-developed for a number of species, especially in the mouse, methods for achieving the desired level of transgene expression in appropriate tissues are less well-established. The introduction of DNA into the mammalian genome can ordinarily be achieved most reliably by microinjection or retrovirus-mediated gene transfer. However, the state of the art for transgenics is unpredictable because the method of gene transfer typically relies on random integration of the transgene construct. Insertional inactivation of endogenous genes and position effects (see Wall, 1996, p. 61, paragraph 3) can dramatically influence the phenotype of the resultant transgenic animal. Integration of the transgene near highly active genes or, alternatively, in a transcriptionally inactive region, can influence its level of expression. Furthermore, expression of the transgene and the effect of transgene expression on the phenotype of the transgenic animal depends on the particular gene construct used, to an unpredictable extent. The particular genetic elements required for appropriate expression varies from species to species. Thus, a construct that confers the desired phenotype in a mouse will not necessarily achieve the same result in a rat. Wall (1996) reports that our lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior (p. 61, paragraph 3). This is especially relevant for species in which genetic studies are less advanced than in the mouse. Thus, the species-specific requirements for transgene design introduces an additional level of unpredictability associated with the development of transgenic animals. Furthermore, there are inherent physiological differences between mice, rats, fish, birds, etc. that can affect the phenotype in an unpredictable manner. In the absence of appropriate working examples, the existence of any phenotypic alteration resulting from the introduction of an epitope-tagged TBP transgene construct in a mouse or any other species of animal, is highly unpredictable.

While the species-specific requirements for transgene design are not fully understood, examples in the literature clearly demonstrate that even closely related species carrying the same transgene construct can exhibit widely varying phenotypes. For example, several animal models of human diseases have relied on transgenic rats when the development of mouse models was not feasible. Mullins et al., 1990 produced outbred Sprague-Dawley x WKY rats with hypertension caused by expression of a mouse *Ren-2* renin transgene. Hammer et al., 1990 describe spontaneous inflammatory disease in inbred Fischer and Lewis rats expressing human class I major histocompatibility allele HLA-B27 and human β_2-microglobulin transgenes. Both investigations were preceded by the failure to develop human disease-like symptoms in transgenic mice (Mullins et al., 1989; Taurog et al., 1988) expressing the same transgenes that successfully caused the desired symptoms in transgenic rats.

With regard to Claims 23-25, the specification fails to provide an enabling disclosure for the method of expressing an epitope-tagged TBP in a transgenic animal, including the transgenic mice described in the working examples because, as discussed above, the specification does not offer any guidance for obtaining expression of the protein in any tissue of any animal.

With regard to Claims 26-35, the specification fails to provide an enabling disclosure for the isolation of transcription complexes. The specification does not offer any guidance for purifying epitope-tagged TBP-containing transcription complexes from any tissue of any transgenic animal. The specification points to prior art references where monoclonal antibodies were used to purify epitope-tagged TBP-associated complexes from nuclear extracts from cell lines, including HeLa cells or yeast, thus co-purifying TBP-associated factors (TAFs) of the TFIID complex (p. 4, lines 13-15 and Zhou et al., 1993). However, with regard to the claimed method for isolating a higher order transcription complexes from a transgenic animal, the method is not enabled because the specification does not teach one skilled in the art how to obtain expression of the epitope-tagged TBP protein at a level sufficient to allow for the isolation of TBP-containing complexes.

With regard to the claims directed to and encompassing transgenic mice, methods of making, and methods of using the transgenic mice, the specification fails to provide an enabling disclosure for the transgenic mice, including the disclosed mice, and the contemplated methods, because the method of using the mice requires expression of the protein. The working examples do not demonstrate expression of the epitope-tagged TBP in the mice and the specification does not offer any guidance for obtaining appropriate expression of the protein. Furthermore, the only use contemplated for the transgenic mice is for the isolation of TBP-containing complexes. Thus, the transgenic mice and the methods of making the mice are not enabled because the epitope-tagged TBP must be expressed at a level sufficient to allow for the purification of transcription complexes.

In the preliminary remarks filed March 15, 2002, Applicants argue that the Declaration of Dr. Kirschbaum filed concurrently demonstrates, through Western blot gels, that Applicants were able to demonstrate that the level of expression of hTBP was sufficient to permit isolation and purification of hTBP-containing complexes. Although the Declaration seems to refer to figures, as in Example 1 which refers to the "left lane", no figures are included with the Declaration. The Examiner cannot comment on evidence that is not of record. Furthermore, the Declaration does not describe the protocols that were used for isolating the various complexes. Without this information the Examiner cannot determine if the isolation protocols were carried out in accordance with the teachings of the specification. The Declaration has been fully considered but is not found persuasive due to the deficiencies noted here. In the preliminary remarks Applicants also refer to several pages from Dr. Berglund's thesis. However, Dr. Berglund's thesis is not of record in this application. If Applicants intend to rely on this thesis for supporting evidence it should be made of record in this application.

Given that specific phenotypic alterations cannot be predictably achieved by merely transferring a gene of interest into an animal, specific guidance must be provided to enable the instant invention. The specification must teach those skilled in the art how to make and use the full scope of the claimed

invention without undue experimentation. The claims cover transgenic animals carrying an epitope-tagged TBP transgene under the control of a constitutive or inducible promoter and methods of using the transgenic animals as a source of *in vivo* formed TBP-containing transcription complexes, but the specification does not enable the transgenic animals nor the methods of using them. Given the limited working examples and the upredictability in the art, undue experimentation would have been required to make and use the claimed transgenic animals and practice the claimed methods.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 7-10 are indefinite in their recitation of "introducing said transgene into germline cells of said non-human animal" and "transferring said transfected germline cells to a surrogate mother, and permitting said germline cell to develop into a non-human transgenic animal" because a "germline cell" cannot develop into an animal; only an embryo can develop into an animal. Claim 10 recites introducing the transgene into an embryonic stem cell, but an embryonic stem cell alone cannot develop into an animal upon transfer to a surrogate mother. Likewise, a blastomere (as recited in Claim 9) cannot develop into an animal upon transfer to a surrogate mother. The claims are incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (703) 306-9155. The examiner can normally be reached Monday through Thursday and alternate Fridays from 10:00 AM to 7:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The central official fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to William Phillips, whose telephone number is (703) 305-3482.

Anne-Marie Falk, Ph.D.

Anne-marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER